REMARKS

Claims 1-20, 25-31, 33-35, 37-38, 40-41, 46, 49-54, 56-60, 62-66, 71-74 and 83 have been canceled. Claims 21, 32, 36, 39, 48, 55, 61, 77 and 84 are amended. Claims 91-114 are new. No new matter has been added by the amendments to the claims. After entry of this amendment, claims 21-24, 32, 36, 39, 42-45, 47-48, 55, 61, 67-70, 74-82 and 84-114 will be pending.

Objections to the Specification

Applicants thank the Examiner for amending the Brief Description of Figures 14, 16, 20, 21 and 25 to correspond to the Formal Drawings.

Provisional Double Patenting

The Examiner has provisionally rejected claims 1-90 under the judicially created doctrine of double patenting over one or more claims of copending Application Nos. 09/219,442; 09/247,272; 09/623,725; 09/936,726; 10/060,523; and 10/127,551. Claims 1-20, 25-31, 33-35, 37-38, 40-41, 46, 49-54, 56-60, 62-66, 71-74 and 83 have been canceled. This rejection will be addressed as it is applied to the remaining claims.

Applicants wish to point out that Application No. 09/623,725 has been abandoned. With respect to Application No. 10/127,551, Applicants respectfully traverse. As currently pending, the claims in Application No. 10/127,551 are directed towards DNA. The claims of the instant application are directed towards proteins. With respect to the remaining Applications, Applicants agree to file a Terminal Disclaimer in the instant case over any of the claims as currently pending in any of the cited cases that issue or are allowed prior to allowance of the instant application.

Obviousness-type Double Patenting

Claims 1-90 were also rejected under the judicially created doctrine of double patenting over at least claims 1-15 of US Patent No. 5,932,540. Claims 1-20, 25-31, 33-35, 37-38, 40-41, 46, 49-54, 56-60, 62-66, 71-74 and 83 have been canceled. As applied to the remaining claims, Applicants respectfully submit that the Terminal Disclaimer submitted herewith overcomes this rejection.

Statutory Double Patenting

The Examiner rejected claims 11-14, 84 and 88-90 under 35 U.S.C. §101 as claiming the same subject matter as claims 5, 14 and 15 of US Patent No. 5,932,540. Applicants have canceled claims 11-14 in their entirety and have canceled the offending subject matter from claims 84 and 88-90. Applicants therefore request withdrawal of this rejection.

Scope of Enablement

The Examiner has rejected claims 1-90 under 35 U.S.C. §112, first paragraph as not enabled. Claims 1-20, 25-31, 33-35, 37-38, 40-41, 46, 49-54, 56-60, 62-66, 71-74 and 83 have been canceled. As applied to the remaining claims, Applicants respectfully submit that the amendments to the claims overcome this rejection.

After entry of the current amendment, the pending claims will be directed towards (1) polypeptides having the 350 amino acid sequence of the biologically active, truncated form of VEGF-2; (2) polypeptides having the 350 amino acid sequence of the biologically active, truncated form of VEGF-2, minus the initial methionine; (3) polypeptides having the 350 amino acid sequence of the biologically active, truncated form of VEGF-2, minus the leader sequence; (4) fragments of the 350 amino acid sequence of the biologically active, truncated form of VEGF-2 that retain the conserved 8 cysteines and migrate on a gel at 21kDa; (5) polypeptides having the 419 amino acid sequence of VEGF-2; (6) polypeptides having the amino acid sequence of the 419 amino acid form of VEGF-2, minus the initial methionine; (7) polypeptide having the amino acid sequence of the 419 amino acid form of VEGF-2, minus the leader sequence; (8) a specified fragment (amino acids 47-419) of VEGF-2; and (8) polypeptides having at least 95% identity thereto, which proliferate endothelial cells.

The Examiner asserts that "Applicants have not taught what critical residues must be retained in order to retain the function of the full-length proteins...[or] taught what residues must be maintained in order to produce a protein with the desired functions." (Paper No.021104, page 5). Applicants respectfully disagree.

Contrary to the Examiner's assertion, the specification provides ample guidance as to which amino acid residues are required in order to produce a functional VEGF-2

protein. For example, the specification teaches that VEGF-2 is a member of the PDGF/VEGF family, which shares a conserved motif of eight cysteine residues (Specification, page 10, lines 17-27). FIG. 3 illustrates the amino acid homology between members of the PDGF/VEGF family and highlights the location of the eight conserved cysteine residues.

The specification clearly teaches the significance of the structural motif for the retention of VEGF-2 activity (Specification, page 11, lines 1-7, and FIG. 3). The specification emphasizes that, in addition to the importance of conservation of the eight cysteine residues among the members of the PDGF/VEGF family, the signature consensus sequence for the PDGF/VEGF family, PXCVXXXRCXGCCN, is conserved in VEGF-2 (Specification, page 10, lines 25-27). In light of the teachings of the specification, one skilled in the art would reasonably expect that the conserved motif or signature consensus sequence should be maintained in VEGF-2 fragments in order to retain biological activity.

The specification also provides guidance to the skilled practitioner as to what amino acids can be altered while maintaining the desired activity. For example, Table 1, found on page 39 of the specification, lists conservative amino acid substitutions. At page 37, lines 27-28, the specification describes "substitutions of charged amino acids with another charged amino acid and with neutral or negatively charged amino acids." Also, on page 37, lines 6-10, the specification references Bowie, et al., which describes phenotypically silent amino acid changes. At page 37, line 11-26, the specification teaches that VEGF-2 fragments, derivatives, or analogs may be:

> (i) one in which one or more of the amino acid residues are substituted with a conserved or nonconserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code; or (ii) one in which one or more of the amino acid residues includes a substituent group; or (iii) one in which the mature polypeptide is fused with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol); or (iv) one in which the additional amino acids are fused to the mature polypeptide, such as a leader or secretory sequence or a sequence which is employed for purification of the mature polypeptide or a proprotein sequence; or (v) one in which comprises fewer amino acid residues shown in SEQ ID NOS:2 or 4, *and retains the conserved motif* and yet still retains activity characteristics of the VEGF family of polypeptides. [*Emphasis added*]

Additionally, Applicants submit that at the time the instant specification was filed, it was common in the art to make changes to proteins through substitutions, deletions, insertions, and/or additions. This is supported by references in the specification to publications, such as Bowie, et al. (Specification, page 37, lines 6-10) and Ostade, et al. (Specification, page 38, lines 6-9), which demonstrate the skill in the art at the time the application was filed.

The specification also enables the skilled artisan to determine whether a protein falls within the scope of the claims. Specifically, the specification teaches assays and methods useful for determining whether a polypeptide retains biological activity (See, for example, Examples 5 and 6). Thus, one skilled in the art could readily determine whether a polypeptide fragment retains the claimed activity using assays and methods taught in the specification.

The fact that some experimentation may be necessary to determine whether a polypeptide fragment retains the claimed activity does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985). *See also, Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1376, 1384 (Fed. Cir. 1986). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." M.P.E.P. § 2164.06 (*citing, In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)). Furthermore, under 35 U.S.C. § 112, an inventor is not required to disclose "a test of every species encompassed by their claims," even in an unpredictable art. *In re Angstadt*, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976) (emphasis in original). Finally, enablement is not precluded even if some embodiments of the claimed invention are inoperative. Indeed, the M.P.E.P. states that "[t]he presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled." *See*, M.P.E.P. § 2164.08(b).

Applicants respectfully submit that screening molecules for a desired activity is well within the ability of one of skill in the art. Therefore, taking the teachings in the specification regarding conservative substitutions and the significance of the conserved motif, as well as the methods disclosed for determine whether a particular polypeptide has

the claimed activity, one skilled in the art could easily make the claimed polypeptides without undue experimentation.

For the reasons discussed above, Applicants submit that the specification teaches one skilled in the art to make and use any and all polypeptides encompassed by the claims without undue experimentation. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Written Description

The Examiner has also rejected claims 1-90 under 35 U.S.C. §112, first paragraph as lacking written description. Applicants respectfully traverse.

A patent specification, in order to satisfy the written description requirement, must describe the claimed invention in sufficient detail to allow a skilled artisan to reasonably conclude that the inventor had possession of the claimed invention at the time the application was filed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991).

Applicants submit that the instant specification provides a sufficient description of the claimed invention such that a skilled artisan would reasonably conclude that the inventors had possession of the invention at the time the application was filed. The specification describes distinguishing attributes that are shared by members of the genus. For example, the specification describes a conserved functional motif of eight cysteine residues and the consensus sequence PXCVXXXRCXGCCN (SEQ ID NO:8), which is important in maintaining biological activity, such as endothelial cell proliferative activity (Specification, page 10, lines 17-27).

The specification also provides guidance to the skilled practitioner as to other amino acid modifications, such as conservative amino acid substitutions (Specification, Table 1, page 39) and phenotypically silent amino acid changes (Specification, pages 37-38) that can be made and while maintaining the recited biological activity. Furthermore, at the time the instant specification was filed, it was common in the art to make changes to proteins through substitutions, deletions, insertions, and/or additions.

Therefore, one of skill in the art, from reading the disclosure, could readily envision and identify by specific amino acid sequence the individual polypeptides that have an amino acid sequence at least 95% identical to the claimed sequence which proliferate endothelial cells.

CONCLUSION

Applicants respectfully request that the amendments above be entered. The Examiner is invited to call the undersigned at the phone number provided below if any further action by Applicant would expedite the examination of this application.

If there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. § 1.136, such an extension is requested and the fee should also be charged to our Deposit Account.

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Respectfully submitted,

By _____

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